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(71) Applicant: QUADRANT HOLDINGS CAMBRIDGE LIMITED [GB/GB]; 1 Mere Way, Ruddington, Nottingham NG11 7JS (GB).

(72) Inventors: COLACO, Camilo; 107 Foster Way, Cambridge CB2 2JN (GB). MARTYN, Glen, Patrick; Quadrant Holdings Cambridge Limited, 1 Mere Way, Rudddington, Nottingham NG11 6JS (GB).

(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

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(57) Abstract

Spun filamentous carbohydrates are obtained from anhydrous carbohydrates with or without added bioactive excipients. The product can be formed into a confectionery or used as a delivery vehicle for active agents.

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FILAMENTOUS AMORPHOUS CARBOHYDRATE COMPOSITIONS AND THERAPEUTIC DELIVERY VEHICLES COMPRISING THEM

Field of the Invention

The present invention relates to methods of making filamentous anhydrous carbohydrate compositions and to the products obtained thereby. The compositions are suitable for consumption as a confection and can also be used as therapeutic delivery vehicles, particularly for the oral delivery of therapeutic and/or bioactive substances.

Background of the Invention

The most common pharmaceutical dosage form is the tablet. The main limitations of tablets are poor patient compliance, due to their being difficult to swallow and the ineffective dissolution of these dosage forms to release their bioactive contents. In order to obtain rapidly soluble therapeutic delivery formats, a number of approaches have been used, including effervescent tablets using a variety of volatile material-generating systems, chewable tablets and the development of disintegrants and wicking agents.

Therapeutic compositions have been formulated using rapidly-soluble matrices. These are especially useful for oral administration, such as lingual, sublingual or buccal delivery. The current most commercially popular form is described in US-A-4305502 and US-A-4754597, and comprises a rapidly-soluble solid dosage form made by aliquoting a slurry of therapeutic agent, solvent, gelatin and other excipients into preformed depressions. The liquid is then frozen and the solvent removed by sublimation, typically freeze-drying. The resulting tablet has an open porous matrix that dissolves rapidly on contact with saliva at body temperature in the mouth. This dosage format, marketed by R.P. Schererer as Zydis®, has enjoyed commercial success, for instance, as the Feldene® tablets distributed by Pfizer.

This type of delivery vehicle allows rapid dissolution of the delivery vehicle on exposure to moisture. Consequently, the tablet dissolves almost immediately upon contact with mucosal surfaces. Although this format enjoys a large market, it has the drawbacks of containing gelatin and requiring freeze-drying. Gelatin has recently fallen out of favour, due to the potential of contamination by the scrapie virus and its unsuitability for vegetarians. The hygroscopicity of this gelatin formulation also means that Zydis® tablets have to be stored in moisture-resistant packs. On storage, these tablets quickly give rise to an unacceptable, "sticky" mouth-feel resulting from the poor solubility

of gelatin below 37°C that is accentuated by moisture uptake by the freeze-dried gelatin. Freeze-drying is expensive, consuming both time and energy. Additionally, the requirement for freeze-drying in individual pre-formed units to preserve the structural integrity of Zydis® tablets incurs additional costs in special equipment and processing.

EP-A-0357665 describes therapeutic vehicles made from cotton candy. These have the advantages of cost and simpler, more flexible processing, over Zydis® tablets. Cotton candy, or candy floss, is a well-known confection ordinarily made from cane sugar (granulated sucrose) to yield a sticky, filamentous mass of candy.

Methods of making cotton candy are described, for instance, in US-A-3557717. The process generally comprises heating the cane sugar in a vessel to obtain a molten sugar, and spinning the vessel so as to force the liquid sugar through openings in the vessel. The resulting cotton candy is typically wound around a paper wand until a sufficient amount is collected for consumption. Besides its use as a novelty confectionery, the main characteristic of this sugar matrix is that it is rapidly soluble and this property has been utilised to make a number of rapidly soluble pharmaceutical dosage forms.

More specifically, EP-A-0357665 describes the steps of preparing a slurry of therapeutic agent (such as acetaminophen) in a liquid (such as isopropyl alcohol), adding the slurry to a sugar, drying the resulting mixture, and using the dried mixture to make cotton candy by known methods. A number of sugars are given, including maltose, fructose, sorbitol, dextrose, mannitol, sucrose and lactose, although it appears that sucrose is most often the base sugar with others such as lactose or mannose being added in small amounts to improve the final product. The fibrous product may be compacted, to form sheets that can be divided into dosage forms. While the cotton candy-based medicaments are readily-soluble, they must be produced and packaged under conditions of low or no humidity. The results of a packaging test show "that a sucrose carrier produced an unstable product unless it could be stored in an impermeable hermetically sealed enclosure and was produced in a low humidity environment". Although other sugars are noted to be less susceptible to humidity, it is suggested that products containing these sugars be stored in a moisture-proof package or wrapper. Additionally, few pharmaceutical actives can be incorporated into the sugar matrix, thus requiring the active to be added extrinsically to the candy floss before or during compaction to form

the dosage format (see US-A-5567439). Further, as is shown herein, few carbohydrates are suitable for use in producing fibres in a cotton candy machine.

Besides their use in rapidly dissolving tablets, the cotton candy can also be used to form spherical polycrystalline sugars, as described in EP-A-0646650 and EP-A-0656426. The spheroidal polycrystalline products are made in the first instance by subjecting an amorphous sugar made by a cotton candy machine to a mixture of a non-aqueous liquid in which the sugar does not dissolve and water. The resultant spheroidal crystals are then compacted into tablets. The spheroidal crystals have peculiar organoleptic properties which have been exploited in food and confectionery applications. In the second instance, the amorphous sugar is made by a cotton candy machine is subjected to heat and humidity to yield a crystalline product. The method yields rapidly dissolving wafers.

Other rapidly dissolving therapeutic delivery vehicles are described for instance in US-4855326, US-A-5380473, US-A-5387431, US-A-5501861, US-A-5567439, US-A-5762961, WO 93/10758 and WO 96/01367. Other disclosures that relate to spinning substances with one or more sugars are US-A-4873085, US-A-4997856, US-A-5028632 and US-A-5034421.

Trehalose (α-D-glucopyranosyl-α-D-glucopyranoside), is a naturally-occurring, non-reducing disaccharide which was initially found to be associated with the prevention of desiccation damage in certain plants and animals which can dry out without damage and can revive when rehydrated. Trehalose is a common component of the human diet. Following oral ingestion, trehalose is not absorbed intact through the gastrointestinal tract, as only monosaccharides can pass throughout the intestinal epithelium; see Ravich and Bayless (1983) *Clin. Gast.* 12:335-356. Trehalose is metabolised by the enzyme trehalase into two molecules of glucose. Trehalose is a normal constituent of most mammalian bodies, including humans, and has been identified in human serum, lymphocytes and liver, but is principally located in the brush border of the intestinal tract and the renal proximal tubules. Trehalase is a membrane-bound protein of the human and animal intestinal tract.

Trehalose has been shown to be useful in preventing denaturation of proteins, viruses and foodstuffs during desiccation. See, for example, US-A-4891319, US-A-5026566 and US-A-5149653.

A method of making an anhydrous form of trehalose is described in EP-A-0600730. This method involves heating a trehalose syrup in the presence of a seed crystal and recovering the anhydrous trehalose. This form of trehalose is used as a desiccant.

Summary of the Invention

In evaluating the properties of trehalose, it has been attempted to make cotton candy of this sugar, to produce rapidly-soluble sugar matrices. Commercial trehalose (supplied as the dihydrate) gives a very low yield of poor quality floss. However, following the processing of trehalose to anhydrous trehalose, the technique surprisingly gives a high yields of good quality floss. This is also the case with other hydrated sugars. Most importantly, the incorporation of active agents into candy floss made from any sugar apparently requires the making of anhydrous formulations prior to making the floss.

The present invention encompasses methods of making spun filamentous carbohydrate compositions. The methods include the steps of obtaining an anhydrous carbohydrate; adding excipients, if any, in an anhydrous state, to the carbohydrate; heating the carbohydrate, or mixture of carbohydrate and excipient(s), to form a substantially homogeneous melt; and spinning the melt to form a filamentous product.

In another embodiment, the carbohydrate and excipients are premixed in a liquid (in which one or more of the components may be soluble); brought out of solution in an anhydrous state; and then melted and spun to form a filamentous product.

In another embodiment, a hydrated excipient is added to a carbohydrate (either hydrated or anhydrous), treated to render the mixture anhydrous, heated to form a substantially homogeneous melt and spun to form a filamentous product. If the excipient does not render the melt more than about 1-2% hydrous, the mixture need not be treated to render it anhydrous.

The invention further encompasses the compositions obtained by the methods described herein.

In one embodiment, the product is a confectionery product and the excipients may include flavouring agents, food dyes, stabilisers and the like.

In another embodiment, the product is a therapeutic delivery vehicle and the excipients further comprise biologically active agents such as drugs.

In another embodiment, the spun fibres are compressed to form sheets. The sheets can optionally be divided into single or multiple dosage units.

In another embodiment, the spun fibres are processed to yield spheroidal polycrystalline, microcrystalline or amorphous microparticles or nanoparticles for organoleptic or pharmaceutical applications.

A wide variety of bioactive materials are suitable for use in accordance with the present invention, including, but not limited to, therapeutic (including prophylactic) agents. The delivery vehicle and methods of the present invention provide for a variety of dosing schemes for delivery of the bioactive material and are suitable for both veterinary and human applications.

Description of the Invention

As indicated above, it has been found that hydrated carbohydrates can be formulated into spun filaments by first rendering them anhydrous. These anhydrous carbohydrates have been found to be particularly useful where otherwise denaturing conditions would render impossible the formulation of dosage forms of bioactive materials. In particular, such conditions include elevated temperatures and the presence of organic solvents. Formulations comprising an anhydrous carbohydrate and a drug are particularly advantageous for drugs, such as cyclosporin A, which are anhydrous or poorly soluble in aqueous solutions.

It has also been found that, for formulations comprising an anhydrous carbohydrate and an excipient such as a bioactive material, it is desirable to have all components anhydrous prior to making spun filaments incorporating the bioactive. This is particularly important for actives that are hydrated, such as cefadroxil, deoxycyclin and cisapride monohydrate, enalaprilat dihydrate, indomethacin, ampicillin, tetracycline and amoxicillin trihydrate and ceftazidime pentahydrate. Most importantly, it has been found that dehydration of the formulations can be conveniently incorporated into a pre-granulation step which also facilitates processing to form a floss by providing not only larger particles for use in the candy floss machines but lower-melting formulations, presumably due to the formation of a predominantly amorphous mixture in the granulation step.

The present invention encompasses methods for making spun filamentous carbohydrates. The methods include the steps of obtaining a substantially anhydrous carbohydrate, melting the carbohydrate, and anhydrous excipients, if any, to obtain a melt and spinning and extruding the melt by any method known in the art.

As used herein, the term "carbohydrates" or "sugars" includes, but is not limited to, monosaccharides, disaccharides, trisaccharides, oligosaccharides and their corresponding sugar alcohols, polyhydroxy compounds such as carbohydrate derivatives and chemically modified carbohydrates, hydroxymethyl starch and sugar copolymers (Ficoll). Both natural and synthetic carbohydrates are suitable for use herein. Synthetic carbohydrates include, but are not limited to, those which have the glycosidic bond replaced by a thiol or carbon bond. Both D and L forms of the carbohydrates can be used. Derivatised anhydrous or hydrophobic carbohydrates are also suitable for use herein. Suitable derivatised carbohydrates include, but are not limited to, carbohydrate esters, ethers, imides and other poorly water-soluble derivatives and polymers. The carbohydrate can be non-reducing or reducing. In general, the anhydrous carbohydrate should have a melting point that is below that temperature at which the excipients might decompose or otherwise break down such that they are no longer effective.

These carbohydrates can be naturally-occurring, can be rendered anhydrous, or can be hydrophobically derivatised carbohydrates (HDCs). Suitable anhydrous carbohydrates are those in which a bioactive material can be dried and stored without losses in activity by denaturation, aggregation or other mechanisms. Prevention of loss of activity can be enhanced by the addition of various additives such as inhibitors of the Maillard reaction, as described in WO-A-96/05809. Preferably, if the bioactive material and/or anhydrous carbohydrate contains carboxyl and amino, imino or guanidino groups, the compositions further contain at least one physiologically acceptable inhibitor of the Maillard reaction in an amount effective to substantially prevent condensation of amino groups and reactive carbonyl groups in the composition. Addition of such inhibitors is particularly preferred in conjunction with reducing carbohydrates, such as glucose, maltose, lactose, fructose, galactose, mannose, maltulose, iso-maltulose and lactulose.

Non-reducing carbohydrates include, but are not limited to, non-reducing glycosides of polyhydroxy compounds selected from sugar alcohols and other straight chain polyalcohols. Other useful carbohydrates include raffinose, stachyose, melezitose,

dextran, sucrose and sugar alcohols. The sugar alcohol glycosides are preferably monoglycosides, in particular the compounds obtained by reduction of disaccharides such as lactose, maltose, lactulose and maltulose. The glycosidic group is preferably a glucoside or a galactoside and the sugar alcohol is preferably sorbitol (glucitol). Examples include maltitol (4-O-β-D-glucopyranosyl-D-glucitol), lactitol (4-O-β-D-galactopyranosyl-D-glucitol), iso-maltulose, palatinit (a mixture of GPS, β α-D-glucopyranosyl-1→6-sorbitol and GPM), and α-D-glucopyranosyl-1→6-mannitol, and its individual sugar alcohol components GPS and GPM.

A substantially anhydrous carbohydrate or carbohydrate/excipient mixture is one that contains less than 2% water by weight. Suitable carbohydrates include, but are not limited to, anhydrous lactose, anhydrous αα , ββ and α β-trehaloses, raffinose, palatinit, GPS, stachyose, mellibiose and mannotriose.

Preferably, the carbohydrate is anhydrous trehalose (AT), palatinit or raffinose. AT refers to any form of αα-trehalose that contains less than about 2% water. The anhydrous forms of trehalose can contain from about 0-2% water and still retain superior properties in forming spun filaments. The forms of AT include anhydrous amorphous trehalose (AAT) and anhydrous crystalline trehalose (ACT). AT powders can contain AAT and/or ACT. Either form or combination thereof is suitable for use herein.

Anhydrous carbohydrates can be purchased or produced from hydrated carbohydrates by any method known in the art. Methods of producing AT from trehalose dihydrate are described for instance in WO-A-96/40077. The methods described therein produce AAT, ACT and mixtures thereof and are suitable for use in obtaining anhydrous forms of other carbohydrates.

The spun fibres can also be made from anhydrous carbohydrates and optionally at least one excipient. In the case of a confectionery, the excipients can be flavorants, colorants and compositions that improve mouthfeel of the product. The product can be eaten as a confection without further processing or can be further processed by any method known in the art to yield a food product.

In the case of a therapeutic delivery vehicle, the excipients can include those found in confectioneries and an amount of a therapeutic (or bioactive) agent sufficient to yield a final product that contains an effective amount of the therapeutic agent. The products

obtained are suitable for use as pharmaceuticals, other medical applications such as diagnostics, environmental applications, agricultural and industrial use. An effective amount of a bioactive agent is one which causes amelioration or palliation of the condition to be treated. Such amounts are known in the art and readily determinable.

Examples of types of bioactive materials that can be used in the vehicle and methods of the invention include any pharmaceutical agents, including, but not limited to, anti-inflammatory drugs, analgesics, antiarthritic drugs, antispasmodics, antidepressants, antipsychotics, tranquilisers, antianxiety drugs, narcotic antagonists, anti-Parkinsonism agents, cholinergic agonists, chemotherapeutic drugs, immunosuppressive agents, antiviral agents, antibiotic agents, appetite suppressants, antiemetics, anticholinergics, antihistaminics, antimigraine agents, coronary, cerebral or peripheral vasodilators, hormonal agents, contraceptives, antithrombotic agents, diuretics, antihypertensive agents, cardiovascular drugs and opioids.

Suitable bioactive materials also include therapeutic agents, whether curative or prophylactic, e.g. any therapeutically effective biological modifier. Such modifiers include, but are not limited to, subcellular compositions, cells, bacteria, viruses and molecules including, but not limited to, lipids, organics, proteins and peptides (synthetic and natural), peptide mimetics, hormones (peptide, steroid and corticosteroid), D and L amino acid polymers, oligosaccharides, polysaccharides, nucleotides, oligonucleotides and nucleic acids, including DNA and RNA, protein nucleic acid hybrids, small molecules and physiologically active analogs thereof. Further, the modifiers may be derived from natural sources or made by recombinant or synthetic means and include analogs, agonists and homologs.

As used herein, "protein" refers also to peptides and polypeptides. Such proteins include, but are not limited to, enzymes, biopharmaceuticals, growth hormones, growth factors, insulin, monoclonal antibodies, interferons, interleukins and cytokines. Organics include, but are not limited to, pharmaceutically active chemicals with amino, imino and guanidino groups. Suitable steroid hormones include, but are not limited to, estrogen, progesterone, testosterone and physiologically active analogs thereof. Numerous steroid hormone analogs are known in the art and include, but are not limited to, estradiol, SH-135 and tamoxifen. Many steroid hormones such as progesterone, testosterone and analogs thereof are particularly suitable for use in the present invention as they are not

absorbed transdermally and, with the exception of a few analogs, are destroyed upon oral administration by the so-called hepatic first pass mechanism. Therapeutic agents prepared by the methods described herein are also encompassed by the invention. As used herein, "nucleic acids" includes any therapeutically effective nucleic acids known in the art including, but not limited to, DNA, RNA and physiologically active analogs thereof. The nucleotides may encode single genes or may be any vector known in the art of recombinant DNA including, but not limited to, plasmids, retroviruses and adeno-associated viruses. Preferably, the nucleotides are administered in the powder form of the solid dose vehicle.

Compositions containing prophylactic bioactive materials and carriers therefore are further encompassed by the invention. Preferred compositions include immunogens such as vaccines. Suitable vaccines include, but are not limited to, live and attenuated viruses, nucleotide vectors encoding antigens, heat shock protein complexes, bacteria, antigens, antigens plus adjuvants, haptens coupled to carriers. Particularly preferred are vaccines effective against diphtheria, tetanus, pertussis, botulinum, cholera, Dengue, Hepatitis A, C and E, hemophilus influenza b, herpes virus, *Helicobacter pylori*, influenza, Japanese encephalitis, meningococci A, B and C, measles, mumps, papilloma virus, pneumococci, polio, rubella, rotavirus, respiratory syncytial virus, Shigella, tuberculosis, yellow fever and combinations thereof. Vaccines may also be produced by molecular biology techniques to produce recombinant peptides or fusion proteins containing one or more portions of a protein derived from a pathogen. For instance, fusion proteins containing the antigen of interest and the B subunit of cholera toxin have been shown to induce an immune response to the antigen of interest.

Preferably, the immunogenic composition contains an amount of an adjuvant sufficient to enhance the immune response to the immunogen. Suitable adjuvants include, but are not limited to, aluminium salts, squalene mixtures (SAF-1), muramyl peptide, saponin derivatives, mycobacterium cell wall preparations, heat shock proteins, monophosphoryl lipid A, mycolic acid derivatives, nonionic block copolymer surfactants, Quil A, cholera toxin B subunit, polyphosphazene and derivatives, and immunostimulating complexes (ISCOMs) such as those described by Takahashi et al. (1990) *Nature* 344:873-875. For veterinary use and for production of antibodies in animals, mitogenic components of Freund's adjuvant can be used. As with all immunogenic compositions,

the immunologically effective amounts of the immunogens must be determined empirically. Factors to be considered include the immunogenicity, whether or not the immunogen will be complexed with or covalently attached to an adjuvant or carrier protein or other carrier, route of administration and the number of immunising doses to be administered. Such factors are known in the vaccine art and it is well within the skill of immunologists to make such determinations without undue experimentation.

The present invention encompasses compositions and methods of making the compositions. Although singular forms may be used, more than one anhydrous carbohydrate and more than one biological substance may be present. Determination of the effective amounts of these compounds is within the skill of one in the art.

Methods for preparing spun sugar fibres are known in the art. See, for example, US-A-393043, US-A-4526525 and EP-A-0357665.

Conventional "cotton candy" or "candy floss" spinning equipment can be used. Such equipment is commercially available, for example, from Kando or Econofloss. Alternatively, any equipment that achieves the effect of producing spun fibres can be used. The anhydrous carbohydrate is added to the machine, optionally mixed beforehand with a pharmaceutical compound and/or at least one excipient. Alternatively, an anhydrous carbohydrate and a pharmaceutical compound can be added to the candy floss machine and then mixed. In general, the candy floss machine is operated between 50°C and 250°C. The candy floss machine is operated according to manufacturer's instructions. The spinning process for producing "candy floss" is a melt extrusion process in which the starting material is melted and forced through a set of fine orifices, such as found in a mesh, to yield fine fibres that constitute the floss. The conventional equipment uses a rotating spinning head surrounded by a bowl into which the fibres are spun. In preferred equipment, the melting temperature in the spinning head chamber can be varied and controlled. Spun fibres are then collected and compressed into dosage units, which may be in the form of tablets. Compression or compaction of the fibres can be carried out by any known process, including those described in EP-A-0357665.

The carbohydrate and any excipients must be anhydrous prior to processing into spun filaments. Suitable treatments to render the mixture anhydrous include any known in the art such as making a foamed glass matrix (WO-A-96/40077), freeze-drying, vacuum-drying and spray-drying or any combination thereof. The components can be

combined by mixing the dried carbohydrate and excipient, melting the combination and spinning the melt to form fibres. The components can also be dried from an aqueous solution or suspension of the carbohydrate and the excipient to form an anhydrous mixture by any drying technique known in the art including, freeze-drying, spray-drying, vacuum-drying, spray-chilling, critical fluid-drying and emulsion-drying. The components can also be dried from an organic solution or suspension of the anhydrous carbohydrate and the excipient in a solvent or super-critical fluid capable or rendering the mixture anhydrous. Such a process can further be incorporated into a pre-granulation or granulation step to yield a particle size larger than the orifice in the floss-forming apparatus, thus facilitating the processing of the formulation in the floss-making step. The anhydrous mixtures of carbohydrate and the excipient can then be spun to form a matrix. Alternatively, the components can also be combined by making an amorphous glass as described in WO-A-96/40077. These glasses can then be milled and/or micronised to give microparticles of homogeneous, defined sized which can then be spun to form a matrix. Such processing should generally yield a particle size larger than the orifice in the floss forming apparatus, to facilitating the processing of the formulation in the floss-making step without the need for a pre-granulation step.

The spun filament product can be further processed by any method known in the art. The filaments can be crushed and delivered as powders or made into tablets. The filaments can also be further processed to yield homogeneous crystalline, polycrystalline or anhydrous microparticles by methods including, but limited to supercritical fluid extraction and that described in EP-A-0646650 and EP-A-0656426. If methods such as the latter are used, the non-aqueous liquid is replaced by an aqueous liquid when hydrophobically derivatised carbohydrates are used to make the spun filament. In addition to the active agent, tablets may contain a variety of other components or "excipients" known in the art to form tablets.

The following Examples illustrate the invention.

Example 1

Cotton candy was prepared according to the following protocol. The cotton candy machine (Kando K1 Kandy Floss cotton candy machine; see GB-A-1533012) was filled halfway with ACT (approximately 100 g). The motor was then switched on and the powdered sugar glass heated at element settings between 5 and 9. Residence time in the

spinning head was 2-10 min and a continuous process was maintained by constantly topping up the head. Fibres spun from AT formed a large mass of fine floss [~120 litres], with no evidence of caramelisation in the sugar matrix. By contrast, the use of the same quantity (~100 g) of hydrated trehalose (comercially purchased crystalline trehalose dihydrate) to form candy floss yielded only a minimal volume (>1 litre) of thicker fibres that were filled with sections of caramelised sugar in the filamentous matrix. The fibres formed from AT were stable for at least several months when kept sealed in plastic under ambient conditions. Additionally, the candy floss made from AT did not need protection from ambient humidity and did not become sticky in the presence of such humidity as compared to candy floss made from sucrose.

Example 2

In order to confirm that the formation of candy floss required anhydrous as opposed to hydrated carbohydrate, cotton candy was formed from anhydrous palatinit and palatinit monohydrate and anhydrous raffinose and raffinose pentahydrate. Hydrated sugars were purchased from commercial sources. Anhydrous sugars were produced by heating the hydrated sugars at 90°C under 1 mTorr vacuum for 12-24 hours. Approximately 100 g of the hydrated or anhydrous carbohydrated sugars was loaded into the head of the floss machine and spun at settings between 5 and 9 on the Kando Kandy Floss machine. With the hydrated sugars, a substantial volume of water collected initially on the side of the fibre pan, and then some spatters of molten sugar appeared which flossed slightly. After a few minutes, the floss began to burn and turn brown. No suitable candy floss was formed from the hydrated sugars. By contrast, when the anhydrous sugars were spun in the cotton candy machine as described above, high yields of good quality white fibres, with little evidence of sugar caramelisation, were obtained.

Example 3

In order to investigate the production of candy floss from fine powders that need granulation to facilitate their use in conventional candy floss machines, and further confirm the requirement for anhydrous sugars, cotton candy was formed from anhydrous lactose and lactose monohydrate. Approximately 100 g lactose monohydrate was charged into a bending machine (Kenwood) in order to granulate it. This step was performed because the particle size of the starting material was smaller than the holes of the mesh in the cotton candy machine. Sufficient water was added to bind the powder into

aggregates. This was then mixed on full power/high shear to dissociate the aggregates. A portion was then added to the head of the floss machine and spun on full heat. Initially, a substantial volume of water collected on the side of the fibre pan then some spatters of molten sugar appeared which flossed slightly. After a few minutes, the floss began to burn and turn brown. No suitable candy floss was formed from the lactose monohydrate.

The granulated lactose was then heated at 90°C under 1 mTorr vacuum for 3 hours to produce anhydrous lactose and spun in the cotton candy machine as described above. High quality white fibres were generated with high yield.

Example 4

To examine the incorporation of an active in the floss matrix, fibres were spun from mixtures of AT and the dye Mordant Blue 9 as an active. The formulations used were (i) AT plus dye both as anhydrous solids, (ii) AT plus dye freeze-dried from aqueous solution to give an amorphous trehalose glass incorporating the dye, (iii) AT plus dye vacuum-dried from aqueous solution to give an amorphous trehalose glass incorporating the dye, (iv) AT plus dye spray-dried from aqueous solution to give an amorphous trehalose glass incorporating the dye, (v) AT plus dye granulated using absolute ethanol to yield 3-5 mm particles of water content <1%, and (vi) AT plus dye granulated using aqueous granulation to yield 3-5 mm particles of water content ~8%. In all cases except the last, a good yield of a large mass of fine floss was obtained, with no evidence of caramelisation in the sugar matrix. By contrast, the use of the mix obtained by aqueous granulation mix yielded only a minimal volume of fibres with sections of caramelised sugar in the filamentous matrix. Drying of the mix obtained by aqueous granulation to a water content of <2% significantly improved both the yield and quality of the floss obtained.

Example 5

The fibres formed from AT were added fresh to anhydrous ethanol with continuous stirring. The fibres dissolved instantaneously and a fine powdery precipitate was formed shortly afterwards. The suspension was filtered to remove the ethanol and dried in a fume table to yield a fine free-flowing powder which appeared to be composed of homogeneous 10-15 μm orthorhombic crystals of trehalose. Storage of this powder under ambient conditions of temperature and humidity showed no clumping or aggregation of the powder even after storage for 3 months.

CLAIMS

1. A mass of spun fibres obtainable from molten substantially anhydrous carbohydrate.

2. A mass according to claim 1, wherein the carbohydrate is selected from crystalline trehalose, amorphous trehalose, raffinose, lactose, derivatised carbohydrates and hydrophobically-derivatised carbohydrates.

3. A mass according to claim 1 or claim 2, wherein the carbohydrate is selected from trehalose, raffinose, palatinate, GPS, stachyose, mellibiose, and mannotriose.

4. A composition comprising a mass according to any preceding claim and an excipient.

5. A composition according to claim 4, wherein the excipient is selected from colouring agents, flavouring agents and therapeutic agents.

6. A composition according to claim 4, wherein the excipient is a pharmaceutical compound.

7. A method for preparing a pharmaceutical dosage unit, comprising the steps of:

(a) introducing into a candy floss machine an anhydrous mixture comprising carbohydrate and a pharmaceutical compound;

(b) heating and spinning the mixture to form spun fibres; and

(c) forming the spun fibres into a dosage unit.

8. A method according to claim 7, which comprises adding at least one excipient to the spun fibres.

9. A method according to claim 8, wherein the excipient is as defined in claim 5.

10. A method according to any of claims 7 to 9, wherein the carbohydrate is as defined in claim 2 or claim 3.

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(71) Applicant: QUADRANT HOLDINGS CAMBRIDGE LIMITED [GB/GB]; 1 Mere Way, Ruddington, Nottingham NG11 7JS (GB).

(72) Inventors: COLACO, Camilo; 107 Foster Way, Cambridge CB2 2JN (GB). MARTYN, Glen, Patrick; Quadrant Holdings Cambridge Limited, 1 Mere Way, Rudddington, Nottingham NG11 6JS (GB).

(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

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(57) Abstract

Spun filamentous carbohydrates are obtained from anhydrous carbohydrates with or without added bioactive excipients. The product can be formed into a confectionery or used as a delivery vehicle for active agents.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 96 03978 A (QUADRANT HOLDINGS CAMBRIDGE ;ROSER BRUCE JOSEPH (GB); COLACO CAMIL) 15 February 1996 (1996-02-15) page 9, line 18 - line 31 page 16, line 13 - line 15 page 19, line 32 -page 20, line 19 page 25, line 26 -page 26, line 21 page 27, line 24 -page 28, line 22 page 36, line 4 - line 27 page 47 -page 49; example 1 ---	1-10
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